REMARKS

Claims 23, 37, and 42 have been amended to recite that the composition comprises an admixture of the components. Support for this amendment can be found, for example, at page 9, line 34 through page 10, line 10 of the specification. No new matter has been introduced. Applicants respectfully request entry of the above amendments, which raise no new issues that would require further consideration and/or search, and which place the application in better condition for allowance.

Applicants thank the Examiner for the courtesy of a telephone interview on November 12, 2002.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 23, 32-35, 37-40, and 42 under 35 U.S.C. §102(b) over Sanders *et al.*, U.S. Patent No. 5,766,605. The Examiner asserted that since botulinum toxin, a local anesthetic, and a local vasoconstrictor "are administered immediately sequentially, the composition is anticipated and formed in the nares of the dog."

The Sanders *et al.* patent does not disclose a composition containing an admixture of botulinum toxin with a local anesthetic agent and/or a local vasoconstrictive agent as recited in amended claims 23, 32-35, 37-40, and 42. Rather, the Sanders *et al.* patent discloses a method for the control of autonomic nerve function that involves administering a therapeutically effective amount of botulinum toxin such that denervation of the neurons is achieved. In the cited passage of the Sanders *et al.* patent (column 8, lines 21-31), a sedative, a decongestant, a local anesthetic, and botulinum toxin were sequentially administered. Applicants disagree with the Examiner's assertions that the decongestant, local anesthetic, and botulinum toxin were administered "immediately" sequentially. Sanders et al. do not indicate that the decongestant, local anesthetic, and botulinum toxin were administered "immediately" sequentially. Further, in clinical practice for removing polyps, physicians typically wait 10 minutes after applying decongestants (e.g., neosynephrine, a vasoconstrictor) and local anesthetics to ensure optimal levels of anesthesia and vasoconstriction before proceeding. See, page 824 of "Atlas of Head & Neck Surgery—Otolaryngology," Eds. Bailey et al., 1996, Lippincott-Raven Publishers (copy enclosed). Thus, the Sanders *et al.* patent does not disclose compositions containing admixtures

of botulinum toxin and a local anesthetic and/or a local vasoconstrictor. Therefore, the Sanders *et al.* patent does not anticipate the claimed compositions, and the Examiner is requested to withdraw the rejection under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 23 and 32-43 under 35 U.S.C. § 103(a) as being unpatentable over Sanders *et al.*, U.S. Patent No. 5,766,605. The Examiner asserted that Sanders *et al.* "teach a composition comprising the decongestant neosynephrine® (phenylephrine, a vasoconstrictor), xylocaine® spray (lidocaine) and type A botulinum toxin. All ingredients were administered to the right and left nasal cavities of anesthetized dogs." The Examiner further asserted that although the Sanders *et al.* patent "does not teach the composition to be mixed in a container" and "does not teach the vasoconstrictor epinephrine specifically," it would have been obvious "to mix the ingredients together in a container" with the motivation from Sanders *et al.* that the ingredients are useful when mixed together in the nasal cavities of a dog." Applicants respectfully disagree.

The Sanders et al. patent does not teach or suggest a composition containing a botulinum toxin, a local anesthetic, and/or a local vasoconstrictor. Instead, the Sanders *et al.* patent provides a method for the control of autonomic nerve function. In the cited passage of the Sanders *et al.* patent (Example IV, column 8, lines 21-37), experiments were done to confirm that botulinum toxin is an effective long-term therapy for vasomotor rhinitis, which is characterized by "a copious flow of clear, watery secretions" that result from excessive parasympathetic activity. See column 1, lines 37-41 and column 7, lines 22-26 of the Sanders *et al.* patent. More particularly, in Example IV of the Sanders *et al.* patent, each nasal cavity of an anesthetized dog was given five drops of the decongestant neosynephrine then sprayed with 4% xylocaine spray. Botulinum toxin A then was administered only to the left nasal cavity using sterile gauze packing. Saline-soaked gauze packing was placed in the right nasal cavity. After one hour, the gauze packing was removed from each nasal cavity. Six days later, the dogs were re-anesthetized, and the right and left sphenopalatine ganglia were sequentially stimulated and secretions were collected from each nasal cavity. Decreased secretions were observed in the botulinum-exposed nasal cavity. See column 8, lines 38-60 of the Sanders *et al.* patent.

In contrast to the Examiner's assertions, the experiment described above does not teach or suggest that "the ingredients are useful when mixed together in the nasal cavities of a dog." Sanders *et al.* simply applied the decongestant to clear the nasal passages and applied the local anesthetic to prevent autonomous effects on the nasal mucosa by mechanical irritation. See column 8, lines 61-65 of the Sanders *et al.* patent, which indicate that topically anesthetizing the nasal mucosa relieves the sensation of nasal obstruction, but does not change nasopulmonary airway resistance. Furthermore, as discussed above, in clinical practice for removing polyps, physicians typically wait 10 minutes after applying decongestants and local anesthetics to ensure optimal levels of anesthesia and vasoconstriction before proceeding. See, page 824 and 826 of "Atlas of Head & Neck Surgery—Otolaryngology," Eds. Bailey et al., 1996, Lippincott-Raven Publishers (copy enclosed). Sanders *et al.* overall conclusion is that rhinorrhea and other disorders associated with control of autonomic nerve function can be treated by locally administering botulinum toxin. Sanders *et al.* do not suggest the botulinum toxin should be combined in a composition with a local vasoconstrictor and/or local anesthetic. In view of the above remarks, the Examiner is requested to withdraw the rejection under 35 U.S.C. §103.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicants ask that claims 23 and 32-43 be allowed. As indicated in the Petition for Extension of Time, Applicants authorize the Commissioner to apply the two-month extension of time fee and any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2/10/03

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Version with markings to show changes made

In the claims:

Claims 23, 37, and 42 have been amended as follows:

23. (Twice Amended) A composition comprising an admixture of a botulinum toxin, a local anesthetic agent, and a local vasoconstrictive agent.

37. (Amended) A composition comprising an admixture of botulinum toxin and a local anesthetic.

42. (Amended) A composition comprising an admixture of a botulinum toxin and a local vasoconstrictive agent.

Atlas of Head & Neck Surgery— Otolaryngology

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321. NASAL POLYPECTOMY

Surgical removal of a polypoid intranasal mass

Indications

1. Presence of a mass, with or without nasal obstruction
2. Suspected malignancy
3. Bleeding
4. Lack of response to medical management, including antibiotics for infection and topical or intralesional steroids for inflammation

Special Considerations

1. Bleeding and clotting abnormalities
2. Cardiac instability
3. Full nasal examination with attention to the septum, nasal bones, and upper lateral cartilages for their possible role in obstruction

Preoperative Preparation

1. Routine laboratory studies
2. Bleeding and clotting studies, if the history is questionable
3. Axial and coronal computed tomography (CT) scans of the nasal cavity and paranasal sinuses

Special Instruments, Position, and Anesthesia

1. Headlight or fiberoptic endoscope
2. Nasal snare
3. Suction cautery
4. Supine position, with the head elevated 30°
5. Local or general anesthesia

Tips and Pearls

1. Careful preoperative determination of the origin of the polyp, including a meningocele, encephalocele, nasopharyngeal mass, or septal mass
2. Pathologic consultation with careful histologic examination
3. Meticulous hemostasis

Pitfalls and Complications

1. Incomplete removal may lead to recurrence
2. Mucosal damage may lead to synechiae or sinus ostial obstruction with secondary sinusitis
3. Vigorous bleeding may obscure the surgeon's vision and require cessation of the procedure.
4. Misdiagnosis of an intracranial polypoid mass may lead to intracranial complications or a cerebrospinal fluid leak.

Postoperative Care Issues

1. Packing, if any, should be completely removed within 3 days.
2. Ensure postoperative hemostasis before discharge.
3. Counsel the patient regarding bleeding, packing removal, nasal hygiene, and prevention of nasal abuse.

Reference

Donald PJ. Minor intranasal procedures. Otolaryngol Clin North Am 1973;6:715.

Operative Procedure

With the patient in the supine position and the head elevated 30°, the nasal cavities are inspected. The CT scan is in the operating room for comparison with clinical findings.

Local anesthesia is preferred over general anesthesia, but in either case, great care must be taken to achieve maximal vasoconstriction. The nasal cavity is sprayed with a 1% solution of phenylephrine. Topical anesthetic (up to 4 mL of 5% cocaine) is applied to 0.5-in (12-mm) plain cotton gauze or to cotton balls and used to anesthetize the sphenopalatine ganglion region at the posterior end of the middle turbinate, the anterior ethmoid nerve region superiorly, and the area in which the nasopalatine nerve comes into the floor of the nose through the incisive foramen (Fig. 321-1). Additional anesthetic is placed along the lateral wall of the nose in the region of the base of the polyp. For patients with evidence of cardiorespiratory instability, an anesthesiologist stands by to monitor and support the patient if necessary.

After a 10-minute wait to allow optimal levels of anesthesia and vasoconstriction, the nasal cavity is inspected again. The exact origin of the polyp is identified. The polyp should be presenting in the middle meatus from the maxillary or anterior ethmoid sinuses, in the superior meatus from the posterior ethmoid sinus, or in the sphenoethmoid recess from the sphenoid sinus (Fig. 321-2). If it originates in any other region, the diagnosis of benign inflammatory polyp must be questioned.

The base of the polyp is encircled with the nasal snare, and the snare is gently closed until the base is firmly grasped (Fig. 321-3). The snare is then withdrawn from the nose with the polyp in its grasp. The polyp is submitted for pathologic examination. The area from which the polyp has been removed is inspected for bleeding. Cotton gauze packing that was originally used to induce anesthesia and vasoconstriction can be reinserted temporarily and placed directly on any bleeding sites (Fig. 321-4). If necessary, the temporary packing can be replaced with petrolatum-impregnated gauze or Merocel gauze, which is left in the nose for 24 to 72 hours for hemostasis. A folded 2 × 2 gauze is taped to the upper lip, not to the nasal tip, to absorb any drainage.

A nasal polyp is rarely an isolated phenomenon. More commonly, it is part of a generalized condition known has hyperplastic polypoid rhinosinusitis, which requires more extensive therapy and is discussed elsewhere in this text.

FRANK E. LUCENTE

322. ENDOSCOPIC EXCISION OF ANTROCHOANAL POLYPS

—The removal of inflammatory nasal polyps originating from the maxillary sinus and protruding into the nasal cavity

Indications

1. Nasal obstruction
2. Associated recurrent acute or chronic sinusitis
3. Associated obstructive sleep apnea

Special Considerations

1. Concomitant inflammatory sinus disease
2. Septal deflection limiting exposure and transnasal delivery of the polyp
3. Transoral delivery for large antrochoanal polyps
4. Bleeding diathesis
5. Nasal mass suspected to be an inverted papilloma or malignancy
6. Consider a Caldwell-Luc approach when the anatomy is poorly defined.

Preoperative Preparation

1. Antibiotics for treatment of associated sinusitis
2. Consider systemic steroids to reduce polyp size and nasal inflammation.

Special Instruments, Position, and Anesthesia

1. Nasal endoscopes and sinus instruments, including angled curets and malleable endoscopic biopsy forceps
2. Position the patient supine, with the surgeon sitting to the right or left of the patient's shoulder.
3. Local anesthesia with intravenous sedation or general anesthesia if transoral delivery is anticipated

Tips and Pearls

1. Antrochoanal polyps are often found in the absence of other sinus disease.
2. The anatomy may be significantly distorted by the polyp.
3. Do not strip the maxillary sinus mucosa; its function should be preserved.

Pitfalls and Complications

1. Incomplete removal of the uncinate process limits exposure.
2. Anterior dissection can jeopardize the nasolacrimal duct.
3. Inadequate antrostomy and polyp removal with resultant recurrent disease
4. Patient aspiration of the polyp
5. Postoperative hemorrhage
6. Orbital complications associated with maxillary sinus surgery
7. Paresthesias associated with infraorbital nerve injury

Postoperative Care

1. Meticulous postoperative debridement to prevent synechiae formation
2. Saline nasal irrigation helps to loosen crusts and evacuate dried blood.
3. Continuation of antibiotic coverage in the perioperative period

References

Crook PR, Davis WE, McDonald R, McKinsey JP. Antrochoanal polyposis: a review of 33 cases. ENT J 1993;72:401.

Loury MC, Hinkley DK, Wong W. Endoscopic transnasal antrochoanal polypectomy: an alternative to the transnasal approach. South Med J 1993;86:18.

Myers EN, Cunningham MJ. Modified Caldwell-Luc approach for the treatment of antral choanal polyps. Laryngoscope 1986;96:911.

Operative Procedure

Oxymetazoline (0.05%) is administered intranasally. While visualizing the nasal cavity with a 0° endoscope, a 1% solution of lidocaine with a 1:100,000 concentration of epinephrine is injected at the anterior root of the middle turbinate, anterior to the uncinate process, and at the superior aspect of the inferior turbinate, as in standard endoscopic sinus surgery. The polyp stalk can be injected to provide hemostasis if the nasal portion of the polyp is to be amputated. A greater palatine foramen block is also useful. This is performed with a 2-in (5-cm), 25-gauge needle attached to a 3-mL syringe. The needle is bent 60° to 80° at a position 2.5 cm from the tip. The hard palate is topically anesthetized if the patient is awake. The foramen is identified by palpation and visualization medial to the second molar. It is located approximately 5 mm anterior to the free border of the hard palate. The needle is inserted submucosally in the vicinity of the foramen, and 0.5 mL is administered. After identifying the foramen by probing along the hard palate, the needle is passed into the foramen no further than 2.5 cm; 1 to 2 mL of anesthetic is injected after aspiration. Air or blood return on aspiration signifies improper needle placement.

After the anesthetics and vasoconstrictive agents have had sufficient time to take effect, the nose is inspected using a 0° nasal endoscope. If necessary, the middle turbinate is medialized with a Freer elevator. An endoscopically guided uncinectomy is performed with a sickle knife and straight Weil-Blakesly forceps (Figs. 322-1 and 322-2). Alternatively, a backbiting forceps can be used for this maneuver. The stalk of the antrochoanal polyp may sufficiently widen the maxillary sinus ostium and result in atrophy of the uncinate process.

After the uncinate has been completely removed, the entry point of the antrochoanal polyp into the middle meatus is identified. The size and position of the polyp may prevent access for the creation of a middle meatal antrostomy, and it may be necessary to remove the nasal portion of the antrochoanal polyp to proceed. This can be achieved transnasally by grasping and avulsing the stalk with a large straight Weil-Blakesly forceps or polyp snare. Alternately, transoral removal may be performed by grasping the polyp in the nasopharynx with a curved Kelly or Crile clamp and transecting the polyp intranasally as it emerges from the sinus. Using a McIvor mouth gag facilitates transoral removal. If sufficient access is available, the polyp and stalk may be left intact until the antrostomy is created. This approach facilitates dissection of the antral portion by allowing gentle traction on the stalk.

The maxillary sinus natural ostium is identified with a 30° telescope and a ball-tipped Lusk seeker. Typically, the polyp protrudes into middle meatus through an accessory ostium in the posteric fontanel (Fig. 322-3). Care should be taken to create a wide antrostomy that includes the natural ostium of the maxillary sinus. The posterosuperior edge of the natural ostium is incised using a curved endoscopic scissors or forward-biting punch. The middle meatal antrostomy is widened with a backbiting forceps or forward-biting punch. The limits of the antrostomy are the basal lamella of the middle turbinate posteriorly; the attachment of the inferior turbinate inferiorly; and the orbit superiorly.

Wide access to the maxillary sinus is critical for complete removal of the antral portion of the polyp. The antral portion of the polyp usually has a cystic component that contains a straw-colored fluid. This cystic portion is decompressed during mobilization of the polyp (Fig. 322-4). The 70° telescope is helpful in visualizing the antral origin of the polyp, although an endoscope placed through a trocar in the canine fossa can also be used.

The polyp is grasped near its base with a large 70° giraffe forceps or a malleable endoscopic biopsy forceps and is delivered from the antrum. The point of attachment can be elevated from the underlying bone with frontal recess curets or giraffe forceps. At this point, the rough edges of the antrostomy are smoothed, and any other necessary sinus surgery can proceed.

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